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13. ABSTRACT *(Maximum 200 Words)*

Over the past year, we have identified an additional 241 cases diagnosed from 1999-2001 and 482 controls from the mammography practice and database at the Mayo Clinic. Together with the previous cases identified, we will have approximately 364 cases and 728 controls, instead of the initially proposed 200 cases and 400 controls. All mammograms over the last 10 years have been obtained for all cases to date and progress is continuing on obtaining the mammograms for the remaining controls. Risk factor information has been abstracted on all 364 cases and approximately 217 controls to date. Work on the remaining 511 controls is underway and will take approximately 1.5 additional years to complete. We performed early analyses of percent breast density and dense area from the earliest mammogram and absolute change between the earliest and latest mammograms with breast cancer risk on the 123 cases and 217 controls for which we had complete information to date. These data were presented at the American Association for Cancer Research meetings in April and also will be presented at the DOD meetings in September. The next two years will involve continuation of mammogram retrieval and digitization, chart abstraction, statistical analyses and report writing.

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Introduction

The interindividual variability in breast tissue on mammographic images, as defined by several measures of mammographic breast density, has been shown to be a major risk factor for breast cancer with three to five-fold increases in risk associated with densities greater than 50% (Boyd, 1998). To date, all studies of breast density and cancer have involved only a single measure of breast density taken between 1-16 years before diagnosis. However, as a women ages, her breast density changes, with the greatest changes reported at menopause. It is not known whether a change in breast density or the rate at which this change occurs is associated with breast cancer risk. Our hypothesis is that women who have a slower rate of change from dense to fatty tissue will be at a higher risk for breast cancer than women who change at a greater rate.

To address this hypothesis, over the past year, we have continued the implementation of a case-control study, which aims to identify all incident cases of breast cancer that have occurred between years 1997-2001 in women ages 50 and older, living within 120 miles of the Mayo Clinic, that were screened over the past ten years at the Mayo Clinic. To date, we have identified 364 new breast cancers over this period that are eligible for our study. In addition, we have selected 728 controls (2 controls matched to each case) matched on age, race, menopausal status, distribution of mammograms and month of last appointment for mammogram. We have collected and digitized mammograms and risk factor information over the last 10 years on all 364 cases and 217 (of the total 728 eligible) controls using mammography database and medical record information. Mammograms remain to be retrieved and digitized on 511 controls. Also, chart abstraction for essential information, including weight history, alcohol intake and hormone replacement therapy status, is underway on the remaining controls.

The mammographic images have been digitized for all cases (364) and 217 controls to date. Breast density (both percent density and total area of density) has been estimated using a semi-automated computer algorithm that has been found to be reliable in several studies (Byng, 1994; Byng, 1996) on 123 cases and 217 controls to date. We have performed preliminary analyses of the associations of breast density and dense area from the earliest mammogram on the 123 cases and 217 controls as well as the absolute change between the earliest and latest mammograms with breast cancer risk. Analyses of rate of change for each individual is currently being computed on this subset of cases and controls and will be examined in association with breast cancer, adjusting for baseline breast density and other breast cancer risk factors.

If a change of breast density over time does influence breast cancer risk, these results will provide an important new avenue of research in breast cancer etiology, including identifying high risk individuals for prevention and examining agents that could affect this progression.

Body

The goal of our study is to examine the association between change in breast density over time and breast cancer risk. The emphasis of the second year of this four year study is to ascertain cases and controls from the years 1999-2001, collect their mammograms over the past 10 years, abstract chart data and obtain other data from the mammography database. We are on task to date, having selected and characterized the remainder of cases over the period 1997-2001, selected the corresponding controls and are working on completing the abstraction and digitization of information on these controls. Below is a detailed description of the activities in the second year of our study.

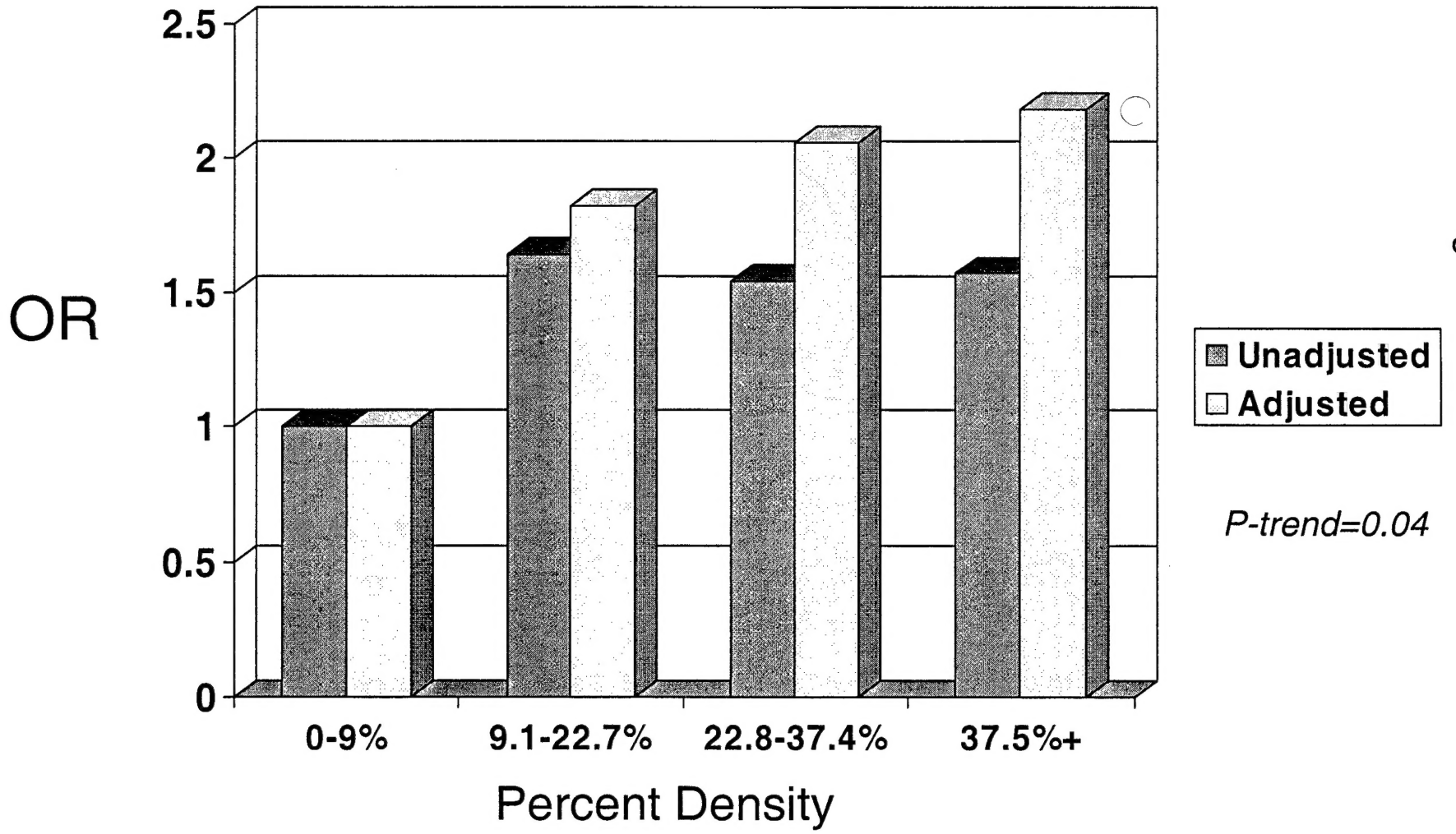
We continued to select cases and controls eligible by our defined criteria over the proposed study period (1997-2001). For cases, eligibility criteria included women aged 50 years or greater, living within the geographic region of the Mayo Health System (~120 miles), who had two or more mammograms performed within the ten years prior to their period of ascertainment. Additionally, at least two of these mammograms must have been performed three years prior to the year of ascertainment. Control women were age-matched within 6 months of the case, will be of the same race and menopausal status, had the same distribution of screening mammograms in the last ten years and had been seen in the Mammography Clinic for a screening mammogram the same month of diagnosis of the breast cancer case. We identified cases and controls through the computerized mammography and pathology databases at the Mayo Clinic, which include detailed clinical and self-reported interview data obtained on women as they come for their mammography appointments.

The first year of data collection involved the identification of 123 cases and 217 controls. The second year has involved primarily identifying and obtaining mammogram and chart information on 241 additional cases, bringing the total to 364 cases. We have also selected the additional 482 controls for the study as well as identifying 29 new controls for those for whom we could not previously identify a 2nd control in the first control selection.

For all these women, risk factor data (including BMI at each mammogram date) was abstracted from the medical histories in an identical manner to the cases previously abstracted. Also, mammograms were digitized and stored on all new cases.

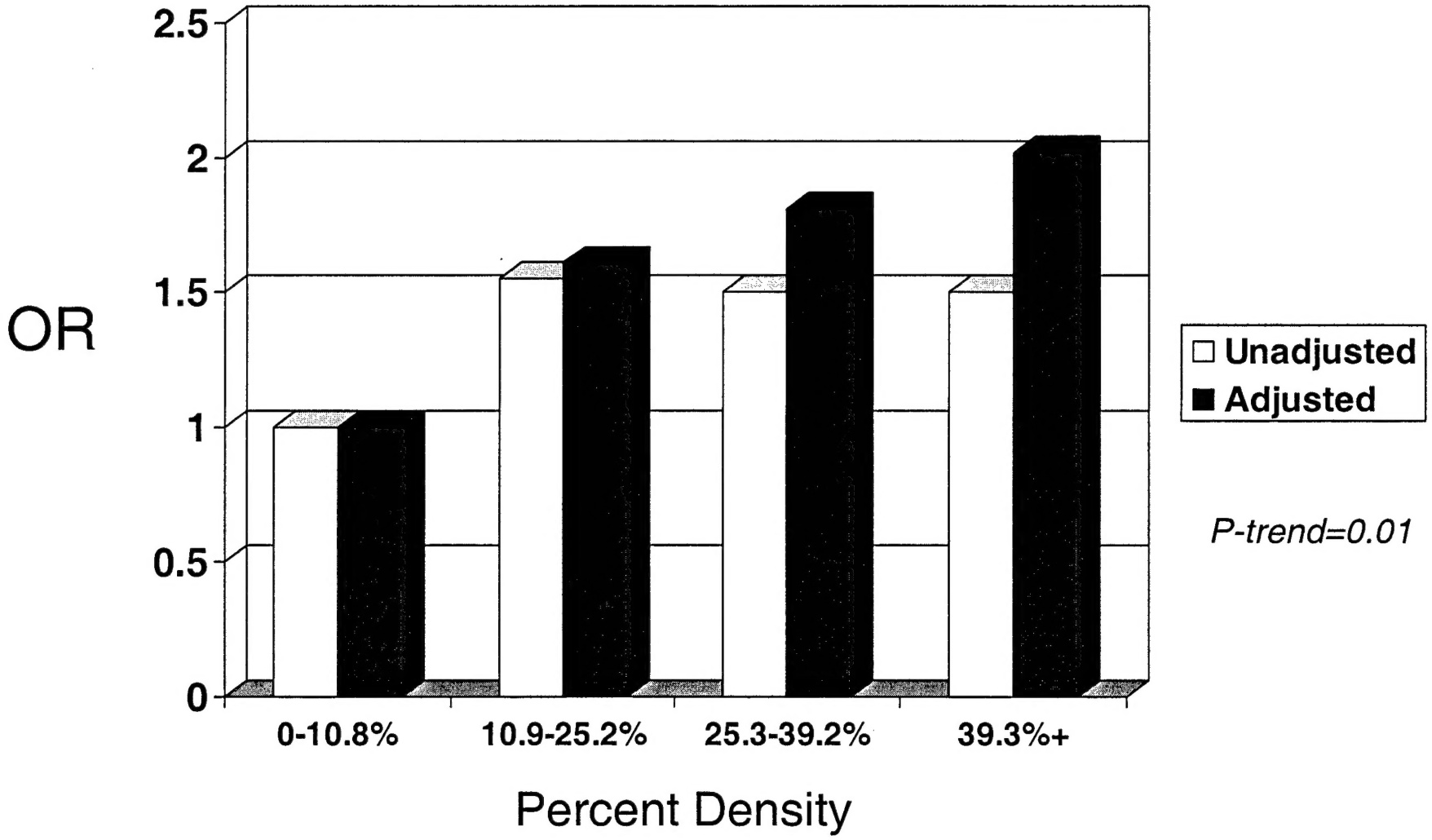
Preliminary analyses have been performed on the first set of cases and controls and presented at the AACR meeting in April, 2002. We have found a significant association between breast density and breast cancer risk, as has been seen by many other groups (See Figures 1a and 1b). We find suggestive association between dense area on the mammogram and breast cancer risk (Figures 2a and 2b). Preliminary results on absolute change in percent breast density and breast cancer risk for both the CC and MLO views show suggestion of an association with breast density for only the MLO view (Figure 3). These data will also be presented at the DOD meeting in September. See appendix for copy of the abstract stating these findings.

Figure 1a. Percent Breast Density and Breast Cancer Risk: MLO View



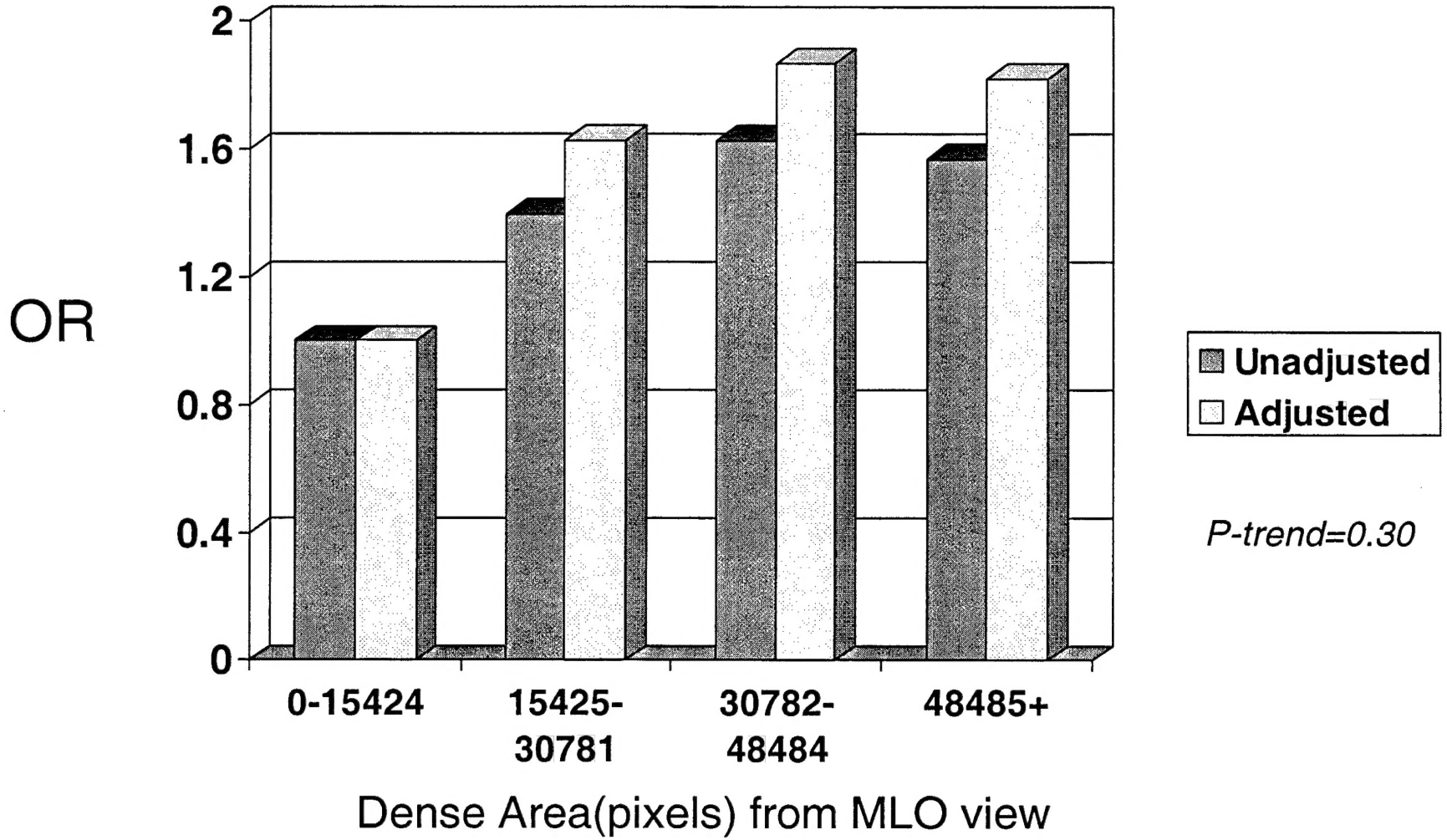
- Adjusted for age at first birth, parity and weight at earliest mammogram

Figure 1b. Percent Breast Density and Breast Cancer Risk: CC View



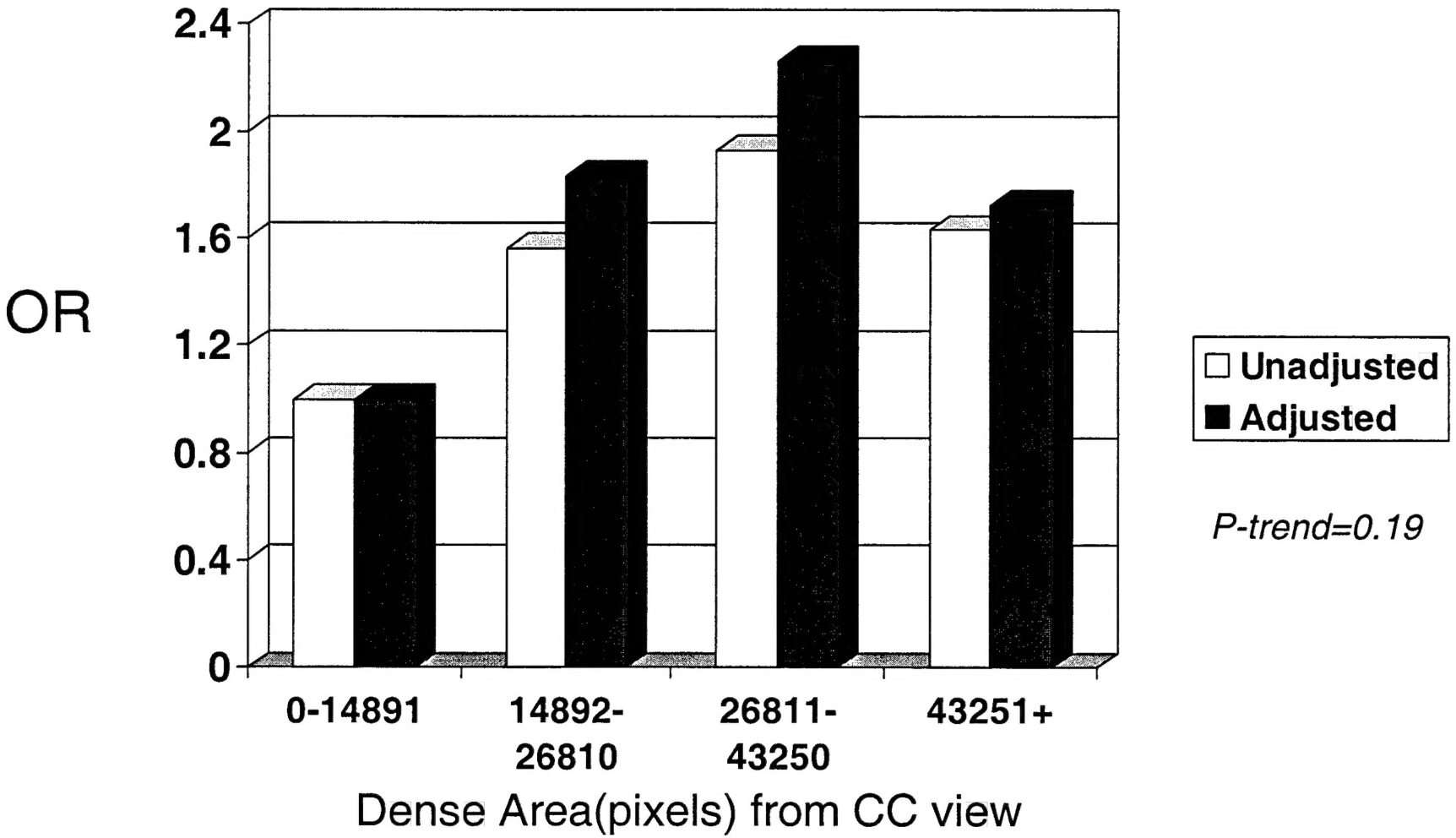
- Adjusted for age at first birth, parity and weight at earliest mammogram

Figure 2a. Dense Area and Breast Cancer Risk: MLO View



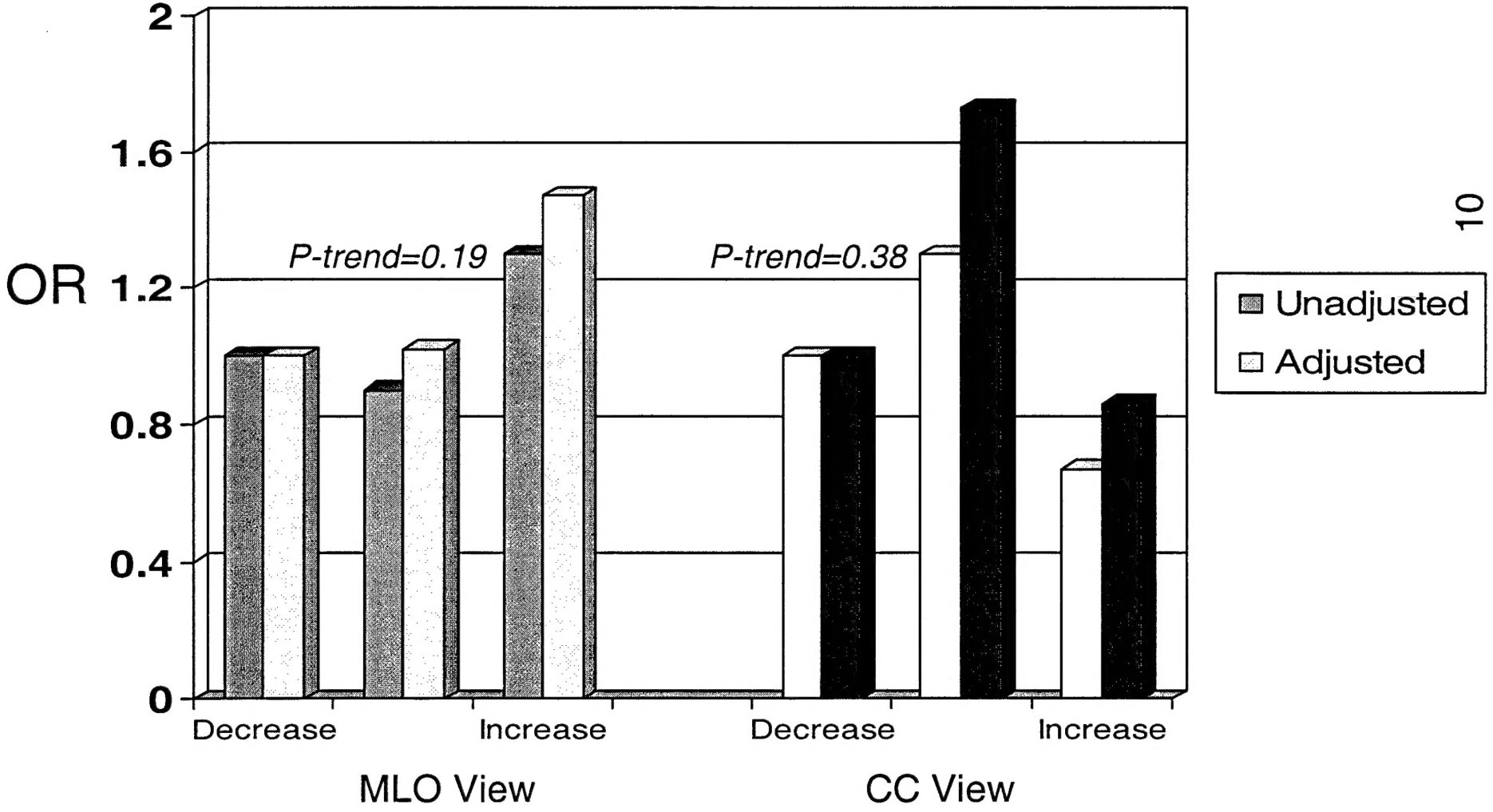
- Adjusted for age at first birth, parity and weight at earliest mammogram

Figure 2b. Dense Area and Breast Cancer Risk: CC View



- Adjusted for age at first birth, parity and weight at earliest mammogram

Figure 3. Change in Breast Density and Breast Cancer Risk: Both views



- Adjusted for weight change and years on HRT

Our accomplishments regarding the statement of work are as follows:

Task 1	Completed
Task 2	Completed
Task3	We are currently working on task 3 for the remaining controls. Since we have increased our numbers of cases and controls for the study, task 3 will require a longer period to complete than proposed. We anticipate completing the abstraction and keying of information on controls (Task 3) by October of 2003.
Task 4	Completed for first set of cases We will finish Task 4 completely (obtaining and digitizing all films on controls) by March of 2003.
Task 5	Completed on all serial mammograms for 123 cases and 217 controls. Percent breast density and dense area have been estimated on the earliest and latest mammograms for the final set of 241 cases. Work is currently underway on the estimation of these measures on digitized mammograms between the earliest and latest mammograms. Task 5 will also require more time than initially proposed, since the sample size for the study has doubled.
Task 6	Initiated on the first set of 123 cases and 217 controls. Data on the association between percent breast density, dense area and absolute change in breast density were presented at the AACR meetings in April (see Appendix). We are currently performing analyses on rate of change over time in this subset of cases and controls.
Task 7	Not applicable

Research Accomplishments

- Selected remaining breast cancer cases between years 1997-2001, abstracted chart data on these women and obtained and digitized mammograms.
- Selected matched controls for cases diagnosed between 1997-2001, currently abstracting chart data and requesting mammograms
- Estimated percent breast density on earliest mammogram from all new cases
- Continued to performed intra and inter reliability studies to evaluate performance of the computer-assisted method.
- Performed preliminary analyses to investigate the breast density, dense area, breast density absolute change and breast cancer association which were presented at AACR meetings
- Currently, performing preliminary analyses of rate of change in breast density over time and breast cancer risk.

Reportable Outcomes

Abstracts

Vachon CM, Sellers TA, Pankratz VS, Wahle A, Wu FF, Brandt KR. Mammographic breast density, dense area and change in breast density with breast cancer risk: A matched case-control study using modern mammography. American Association for Cancer Research, April 2002.

Vachon CM, Sellers TA, Brandt KR, Wu FF, Carston M, Pankratz VS. Change in percent breast density and breast cancer risk. To be presented, Department of Defense Era of Hope Meeting, September, 2002.

Conclusions

The second year of our study continues to be productive, ascertaining the remaining breast cancer cases and identifying controls, abstracting data, digitizing mammograms, estimating breast density and initiating analyses. The only deviation from our Statement of Work is our decision to ascertain more cases and controls than initially proposed. Our decision to do so was based on revised power analysis estimates for the primary aim of change in density and breast cancer risk. When characterizing absolute change in density in our preliminary analyses, we realized that the size of the change in density necessary to achieve the statistical power that we proposed was much larger than we are seeing in our data. Since no one has described breast density change in the population, it is not surprising that our estimate was not representative, and even ambitious. Thus, increasing our sample size is essential to completing our primary aims with adequate power. However, we see the fact that we will be able to complete our aims within the proposed 4-year timeframe and double the number of participants as a major strength of our proposal. With the expanded sample size, we will insure that we have the power to examine our rate of change in breast density with breast cancer risk.

Breast density has consistently been seen to be associated with breast cancer, but there is little understanding of the mechanism. Understanding the association between the dynamic change in breast density over time and breast cancer risk will provide another clue into the etiology of breast cancer as well as target women for prevention efforts. This study is on task and powered to be able to provide information into the change in breast density over time and how this change effects breast cancer risk.

References

Boyd NF, Lockwood GA, Byng JW, Tritchler DL,Yaffe M.J. Mammographic densities and breast cancer risk. Cancer Epidemiol Biomark Prev 1998;7:1133-1144.

Byng J.W, Boyd N.F, Little L, Lockwood G, Fishell E, Jong RA., Yaffe MJ. Symmetry of projection in the quantitative analysis of mammographic images. European J Cancer Prev 1996;5:319-327.

Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. The quantitative analysis of mammographic densities. Phys Med Biol 1994;39:1629-1638.

analysis was used to assess the associations of lifestyle factors and selected food groups with breast density. In univariate analysis television viewing time and frequency of eating high fat snack foods (e.g. chips, nuts, candy, etc.) were positively associated with breast density. Compared to women who view television for up to 1 hour per day, the percent breast density for women who watch television at least 3 hours per day was 5.5 higher (p=0.02). Increasing the consumption of high fat snacks by 7 times per week was associated with a 4.9% higher breast density (p=0.02). Pairwise comparisons revealed that greater television viewing was positively associated with high fat snack foods (chips, nuts, candy, etc p=0.02). Therefore, multivariate analysis was conducted to examine the independent associations of television viewing time and high fat snack consumption with breast density. After adjusting for BMI, hormone use, parity, menopausal status and smoking status, the positive association of breast density with a higher consumption of high fat snacks of 7 times per week became 3.8% (p=0.06). In these analyses, the difference in percent density between women who watched television for at least 3 hours per day compared to women who watch for up to 1 hour per day was 3.5 (p=0.12). Indirectly, these results suggest that behaviors associated with a sedentary lifestyle may contribute to greater breast density and, ultimately, risk of breast cancer.

#1168 Mammographic breast density, dense area and change in breast density with breast cancer risk: A matched case-control study using modern mammography. Celine M. Vachon, Thomas A. Sellers, V. Shane Pankratz, Aimee Wahle, Fang-Fang Wu, and Kathleen R. Brandt. *Mayo Clinic and Cancer Center, Rochester, MN.*

Percent breast density (PD) has consistently been shown to be a risk factor for breast cancer. However, the change in PD over time may be the more relevant predictor of breast cancer risk; women who persist at high levels of PD or increase PD over time may be at greater risk than those who decrease over time. We performed a matched case-control study using the Mammography screening population at the Mayo Clinic to examine the associations of PD, total dense area and change in PD over time with breast cancer risk. We collected, digitized and stored past serial mammograms on breast cancer cases diagnosed through a screening mammogram between 1997-99 and matched controls. Eligible cases were 50+ years at diagnosis, had at least two prior screening mammograms performed two years prior to diagnosis, and lived within a 120-mile radius of the Clinic. Two controls were matched to each case on age, menopausal status, number and distribution of prior mammograms, interval between baseline and final mammogram, final screening exam date and residence. All mammograms were post 1990 and taken at a single institution to reduce possible variability in the PD estimate. The range of time from baseline to the final follow-up mammograms used in these analyses was seven years on average (range 3-10 years). PD and total dense area was read from the most recent (1997-99) and earliest mammogram, using the computerized-assisted thresholding program (Cumulus) developed at the University of Toronto. Risk factor data were abstracted from medical records and a mammography database. Data on 119 cases and 217 matched controls (23 cases had 1 control) were available for these analyses. We present covariate-adjusted analyses on both the craniocaudal (CC) and mediolateral-oblique (MLO) views. PD estimated from both the earliest MLO and CC view was associated with breast cancer, with the highest PD categories associated with a 2-2.2 fold increased risk (CC: OR=1.0, 1.6, 1.8, 2.0 for increasing quartiles, p-trend=0.01; MLO: OR=1.0, 1.8, 2.1, 2.2, p-trend=0.04). There was a suggestive association of dense area with breast cancer risk, although the trends were not statistically significant (CC: OR=1.0, 1.8, 2.3, 1.7, p-trend=0.19; MLO: OR=1.0, 1.6, 1.9, 1.8, p-trend=0.30). For the MLO view, there was some evidence of a greater risk of breast cancer in women who increase PD over time compared to women who decrease over time (OR=1.0, 1.1, 1.5, for women who decrease [< 5% PD], stay the same [within 5% PD] or increase over time [> 5% PD], p-trend=0.19) but this was not seen for the CC view (OR=1.0, 1.6, 0.8, p-trend-0.38). We confirm previous studies of PD and dense area with breast cancer risk; also, we provide novel data on change in PD with breast cancer risk.